

Malaria on the Thai-Burmese border: treatment of 5192 patients with mefloquine-sulfadoxine-pyrimethamine

F. NOSTEN,¹ S. IMVITHAYA,¹ M. VINCENTI,¹ G. DELMAS,¹ G. LEBIHAN,¹ B. HAUSLER,² & N. WHITE³

Multidrug-resistant falciparum malaria is a major health problem along the Thai-Burmese border. From July 1985 until December 1986 a total of 5192 patients with falciparum malaria (1734 males, 3458 females) from this area were given supervised treatment with the combination mefloquine-sulfadoxine-pyrimethamine (MSP). The radical cure rate, assessed 21 days after drug administration, was 98.4% for the first 1975 patients, and 98.8% when assessed at 28 days for the remaining 3217 patients. In 3.8% of cases, parasites were still detected in peripheral blood smears on day 7 after treatment but this had fallen to 0.27% by day 9. Adverse reactions among the first 1975 patients were: vertigo (7.5% of patients), vomiting (5.8%), epigastric pain (0.6%), and transient confusional state (one case). MSP is an effective and well-tolerated drug for the treatment of drug-resistant falciparum malaria; however, delayed parasite clearance may give a false impression of RII resistance.

Mefloquine is effective against both chloroquine- and quinine-resistant falciparum malaria (1-3). It has been used in combination with sulfadoxine and pyrimethamine in order to delay the onset of drug resistance (4), and therefore preserve the efficacy of this important new antimalarial. This combination is now in controlled use for the treatment of proven falciparum malaria in Thailand—where multidrug-resistant *Plasmodium falciparum* has been a particular problem.

Although the situation has improved considerably in Thailand in recent years, *P. falciparum* and *P. vivax* infections remain major health concerns in the heavily forested hills and mountains along the Thai-Burmese border. This region is inhabited by the Karen, a discrete ethnic group living on both sides of the border. Since January 1984, approximately 18 000 Karen people have been displaced from Burma and temporarily resettled in camps and villages situated along the Thai side of the border (Fig. 1). There is intense transmission of malaria in

the areas where these camps are situated. In March 1980, "Médecins sans Frontières" began a programme of medical assistance to this population, and it soon became apparent that malaria was the most important health problem. During 1985 increasing resistance to sulfadoxine-pyrimethamine^a and quinine, as well as poor compliance with the quinine-tetracycline regimen, prompted us to change to mefloquine-sulfadoxine-pyrimethamine for the treatment of falciparum malaria. We report here the results obtained since July 1985 with the latter therapeutic regimen.

MATERIALS AND METHODS

Patients

Three different Karen ethnic groups live together in the villages described in this study. All of the 18 000 displaced Karen people are located in ten open camps: some live in small groups (around 400 inhabitants), but in two of the camps there are more than 2000 inhabitants, and in one (Shoklo) more than 6000. Most of the camps are situated in the mountainous jungle, where the conditions are suitable for the principal anopheline mosquito vectors of malaria to

¹ Médecins sans Frontières, Paris, France.

² WHO, Ministry of Public Health, Malaria Division, Bangkok, Thailand.

³ Tropical Medicine Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, England and Bangkok Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand. Correspondence should be sent to Dr White at the latter address.

^a Fansidar (Hoffmann-La Roche, Basle, Switzerland).

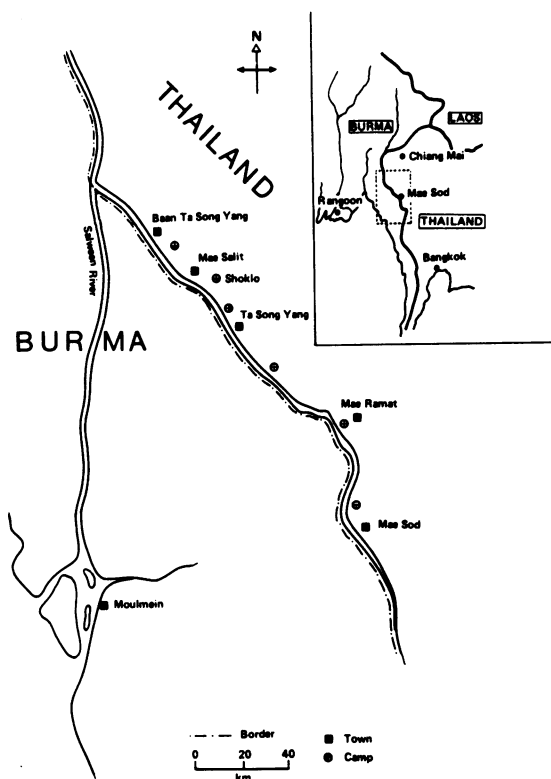


Fig. 1. Location of principal study site camps.

breed. Malaria is a major cause of morbidity and mortality and the single most important infectious disease among the Karen.

Malaria transmission

In order to estimate malaria transmission within the camps, a 4-month survey was performed which documented all cases of *P. falciparum* malaria in babies under 11 months. A standard form was completed for each case. This included details of the infection and of recent travel by the mother. During this period, 63 babies who had never left the camps had positive blood smears. These findings confirmed significant transmission of malaria in the Karen camps and prompted us to institute measures to interrupt it by distributing mosquito nets, educating the population about malaria, and by annual spraying with residual insecticide.

Malaria treatment

All patients with suspected malaria were seen in clinics that were supervised either by a doctor or

a trained nurse and had facilities for blood-film microscopy. Patients were treated only if asexual forms of *P. falciparum* parasites were demonstrated on peripheral blood films. In addition, pregnant women were seen at regular antenatal clinics and blood films routinely examined in all cases of fever. The first protocol used for the treatment of falciparum malaria was administration of quinine (30 mg/kg body weight/day) for 3 days and tetracycline (25 mg/kg body weight/day) for 7 days (Q3, T7). However, when the number of clinical failures (patients with persistent symptoms of malaria and positive blood smears 2 or 3 days after the last day of treatment) reached 20% of those treated, a new regimen consisting of quinine (30 mg/kg body weight/day) and tetracycline (Q7, T7) was given for 7 days. An additional single dose of primaquine (45 mg) was given on the seventh day. Cases of *P. vivax* were treated with chloroquine (25 mg/kg body weight/day) for 3 days and with a single dose of primaquine.

Compliance with the Q7, T7 regimen was poor, and so in February 1985 we requested the permission of the Thai Ministry of Public Health to change our therapeutic regimen to mefloquine-sulfadoxine-pyrimethamine (MSP). Since it was possible to satisfy the strict criteria for use of MSP in Thailand, i.e., parasitological confirmation of the diagnosis and close supervision of drug administration, permission was granted, and this regimen was used for the first-line treatment of falciparum malaria from July 1985 onwards. The preparation used contained sulfadoxine (500 mg), pyrimethamine (25 mg), and mefloquine (250 mg) in each tablet.^b The study followed WHO recommendations, designed to minimize the risks of developing drug resistance, and was supervised throughout by a physician and a laboratory technician. MSP was used only for curative treatment of slide-positive falciparum malaria and not for malaria prophylaxis. Exclusion criteria were: body weight less than 5 kg, pregnancy, severe malaria requiring parenteral therapy, fever above 41 °C, heavy parasitaemia (>200 000 parasites/ μ l), impairment of consciousness, oliguria, severe anaemia, uncontrollable vomiting, severe malnutrition (less than 70% weight-for-length), and allergy to sulfonamides. In these cases, quinine was given intravenously and the Q7, T7 regimen was used when oral therapy was substituted. Young children and pregnant women did not receive tetracycline.

Drug administration

The dosage regimen used is shown in Table 1.

After documentation of clinical details, MSP was given to patients by the nursing or medical staff.

^b Fansimef (Hoffmann-La Roche, Basle, Switzerland).

Table 1. Doses of mefloquine-sulfadoxine-pyrimethamine administered in the study

Patient's weight (kg)	No. of tablets	Amount of mefloquine (mg)
5-10	½	125
10-20	1	250
20-30	1½	375
30-40	2	500
40-45	2½	625
>45	3	750

Patients were observed for an hour after swallowing the drug to ensure that the dose was not regurgitated or vomited. If vomiting occurred, the dose was repeated. A single dose of primaquine (0.9 mg/kg body weight) was given to all patients the same day or the day after treatment with MSP.

Follow-up

Blood smears were checked on day 0 (day of diagnosis and treatment) and subsequently on days 7 and 21 (follow-up study). From 1 January 1986 onwards the final follow-up check was changed from day 21 to day 28. At each visit the patients were questioned about any adverse effects they had experienced. Those with persistent positive blood smears on day 7 were actively rescreened on day 9 and, if still positive, were given quinine and tetracycline (Q7, T7).

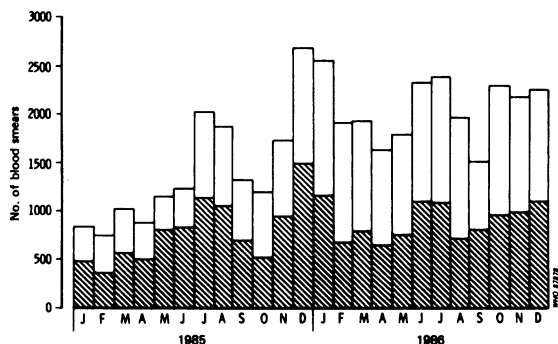


Fig. 2. Number of blood smears examined during 1985-86 and the proportion that were positive (shaded area) for asexual malaria parasites in subjects attending health clinics in the study area.

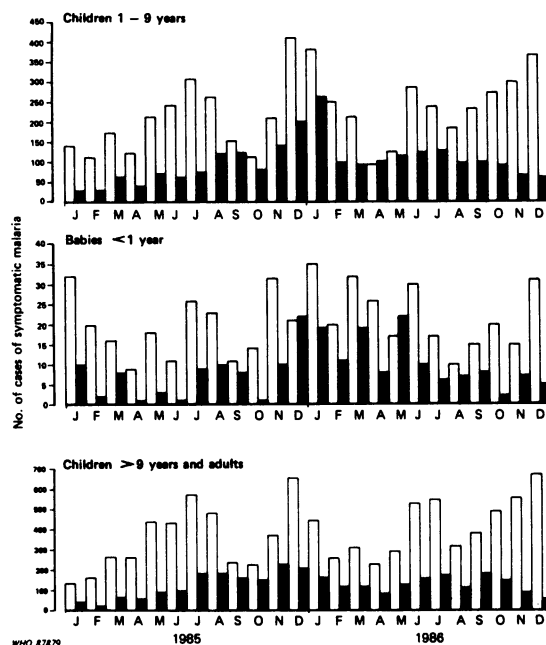


Fig. 3. Stratification of symptomatic malaria cases by age. Open blocks: *Plasmodium falciparum*. Solid blocks: *P. vivax*.

Statistical analysis

Proportions were compared by the χ^2 test with Yates's correction.

RESULTS

Prevalence of malaria

The number of malaria patients who attended the health clinics over the 24 months from January 1985 to December 1986 is shown in Fig. 2, and the data stratified by age are given in Fig. 3. The proportion of malaria infections caused by *P. falciparum* was 79.5% over this period; *P. vivax* was responsible for 25.1%, while 5.3% were mixed infections. Also, 20 cases of *P. malariae* were reported. In order to estimate the point prevalence of malaria in the camp population, a survey was completed in July 1985. Blood smears were taken on a single day from a randomly chosen sample of 377 people from a camp whose total population was 1915: 60 of the 377 smears (15.9%) were positive for malaria parasites, of which 52 (86.6%) were *P. falciparum* and 10

(16.6%) were *P. vivax* (two were mixed). There was a significant difference between the prevalence of positive blood smears in adult males (20 out of 86) compared with that in adult females (17 out of 133; $P < 0.005$). Overall, these data indicate a prevalence of malaria in this population of between 12% and 20% (95% confidence limits) at the time of the study.

Symptomatic malaria

Between July 1985 and December 1986, 5192 patients were diagnosed as having malaria and were treated with MSP. Of these, 1734 were male and 3458 female. There were 1125 children less than 5 years old. Mixed infections occurred in 10.4% (539) of the patients. Patients were asked to return to the clinic for follow-up after 7 days, but 1859 (35.8%) did not do so; of the 3333 who did attend, 3207 (96.2%) had negative smears, while 126 patients were positive (103 had *P. falciparum*, two had mixed infections (2), and 21 had *P. vivax* infections). Of the 105 patients who were still positive for *P. falciparum* or mixed infections on day 7, 96 had negative smears on day 9, without being given additional treatment. Thus, in 2.9% of the patients who presented for follow-up, the parasite clearance time was between 7 and 9 days after administration of MSP. Only nine (0.27%) patients were considered true treatment failures and they were successfully treated with the Q7, T7 regimen.

Of the 189 patients who returned for follow-up 21 days after administration of MSP, 186 had negative smears, i.e., the radical cure rate on day 21 was 98.4%. Although they had been negative on day 7, three patients had smears that were positive on day 21 (two were positive for *P. falciparum* and one for *P. vivax*). The two cases of *P. falciparum* were both symptomatic and were successfully treated with the Q7, T7 regimen.

From 1 January to 31 December 1986, patients were followed up on day 28 instead of day 21, and the radical cure rate was 98.8% (1687 out of 1707 patients). In 20 cases, blood smears were positive on day 28 (13 patients had *P. falciparum*, 6 had *P. vivax* and one had *P. malariae* infection). All were successfully treated with the Q7, T7 regimen or chloroquine.

Fatal cases

During the 18 months from July 1985 to December 1986, there were 42 deaths from falciparum malaria in the study area (eight deaths occurred among children aged under 1 year, 16 among 1–4-year olds, 10 among the 5–14-year olds, and eight among persons over 14 years of age). All but one of the deaths (a pregnant woman) occurred between May

and December 1986 (the rainy season extends from May to October). The fatal cases had all been treated with intravenous quinine.

Malaria in pregnancy

In 1984, 58 of the 120 (48.3%) pregnant women under antenatal supervision in the study area developed malaria during pregnancy. Also, in a prospective study between September and December 1986, 143 pregnant women were screened weekly for malaria parasites. Forty out of these women (27.9%) were positive for asexual forms of *P. falciparum* at some time during the pregnancy and all were treated with quinine (10 mg/kg body weight three times daily for 7 days).

Adverse effects

The following side-effects were documented in the 1975 patients treated between July and December 1985: 150 cases (7.6%) of vertigo, 116 cases (5.9%) of vomiting; 12 cases (0.6%) of epigastric abdominal pain; and one of confusional state. No rashes were reported. Eleven of the adverse reactions were mild and none required specific treatment. Vertigo was maximal 2–4 hours after administration of MSP. Of the 116 patients who vomited, only 8 did so within an hour of receiving the drug and required another dose. None of them had positive smears on day 7 or day 21, and there was no relationship between the incidence of vomiting and the number of tablets swallowed. None of these adverse effects were considered to be clinically serious. A 42-year-old male patient, who apart from malaria had been well, became acutely confused and disorientated 24 hours after receiving 3 tablets of MSP. At this time his peripheral blood smear was negative and he was afebrile. His confusional state resolved spontaneously in 2 days.

DISCUSSION

In this study we were able to monitor the effects of malaria and its response to treatment with MSP in a relatively large number of people living in an area of high malaria transmission. Since all the subjects had recently migrated to the area, there was a broad spectrum in the background level of malaria immunity, i.e., some would have come from areas of intense malaria transmission, whereas others would have originated from areas with little or no malaria. There was consequently considerable variability in the clinical response to infection, which ranged from asymptomatic to lethal. Although there was evidence that malaria was acquired outside the camps (there

was a significantly higher prevalence of positive blood smears among the relatively mobile young adult males), there was also considerable transmission in the camps themselves, as reflected in the high incidence of malaria among babies under 1 year of age. Transmission occurred throughout the year, but, as previously reported from other parts of Thailand (5), the incidence of symptomatic malaria was bimodal, with peaks in the rainy season (August) and at the beginning of the dry season (December).

MSP was a highly effective treatment for falciparum malaria in the study area, where drug resistance is a major problem and compliance with regimens that contain quinine is poor. Although a large number of patients did not return for follow-up, it is very unlikely that many of them developed symptomatic malaria that remained unknown to the medical assistance programme, since there was no other source of health care in these isolated camps. Of the 3333 patients who did return for follow-up on day 7, 105 (3.15%) still had positive blood smears for *P. falciparum* or mixed infection, despite resolution of their symptoms. However, only nine of these patients had positive smears 2 days later on day 9 and required treatment with quinine and tetracycline. Thus, the efficiency of MSP increased from 96.8% on day 7 to 99.7% on day 9. This is presumably explained by slow parasite clearance in some patients, although it is not clear why this should have been so. Possibly this group of patients were infected with more resistant parasites or, because of host pharmacokinetic factors, had relatively low blood concentrations of mefloquine. Alternatively, the positive blood smears could result from delayed clearance of red blood cells containing dead parasites. Irrespective of the reason for the delay in parasite clearance, it is clear from the results that the seventh day after administration of MSP is too early to assess the parasitological response to the drug. Asymptomatic patients who have positive blood smears on day 7

should not be treated, but rechecked 3 days later.

A single dose of MSP is a generally well-tolerated antimalarial regimen. Acute neuropsychiatric reactions have previously been noted (1) and appear to be an unpredictable but important adverse effect of mefloquine. Otherwise there were no clinically apparent adverse cardiovascular effects and no other serious toxic reactions. Vomiting was less common in this series than has been reported previously. Nausea and vomiting are important adverse effects of mefloquine and commonly present physicians with a therapeutic dilemma—drug absorption is unpredictable, and it is often unclear whether adequate antimalarial therapy has been given. However, with a single dose therapy the risks of inadequate treatment outweigh those caused by minor toxic reactions, and therefore patients who vomited within an hour were given a second full dose of MSP. This interval was chosen arbitrarily in the absence of data on mefloquine absorption in febrile nauseated patients, but so far we have encountered no evidence of toxicity with this schedule.

Overall, the incidence of minor side-effects was approximately 13%. Despite the large number of patients in this study, the sample is not of sufficient size to exclude a low incidence of serious adverse reactions to the sulfadoxine component. The incidence of cutaneous reactions to MSP in Thailand is approximately 1 in 6300 (12 cases out of 76 000 treatment doses; B. Hausler, personal communication, 1986), and the mortality associated with sulfadoxine-pyrimethamine among travellers who received antimalarial prophylaxis has been estimated as between 1 in 11 000 and 1 in 26 000 (6). In conclusion, the simplicity of administration and excellent efficacy of MSP make it a preferable alternative to the current quinine-tetracycline regimen for the treatment of malaria, but more data are needed to determine the incidence of its serious toxic effects.

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RÉSUMÉ

LE PALUDISME À LA FRONTIÈRE BIRMANO-THAÏLANDAISE: TRAITEMENT DE 5192 MALADES PAR L'ASSOCIATION MÉFLOQUINE-SULFADOXINE-PYRIMÉTHAMINE

La prévalence, la transmission et la réponse au traitement du paludisme à *Plasmodium falciparum* polypharmac-

résistant a été étudiée dans une population d'environ 18 000 personnes déplacées résidant temporairement dans des

camps situés le long de la frontière birmano-thaïlandaise. Dans cette région, la transmission du paludisme se fait tout au long de l'année et l'incidence du paludisme symptomatique montre une distribution bimodale, avec un pic en août (saison humide) et un autre en décembre (saison sèche). Entre juillet 1985 et décembre 1986, on a administré, sous surveillance médicale, un traitement par l'association méfloquine-sulfadoxine-pyriméthamine (MSP) à 5192 malades (1734 hommes et 3458 femmes) présentant un paludisme symptomatique à falciparum. Parmi eux, 1125 (22%) étaient des enfants de moins de 5 ans. Au cours de cette période, le paludisme à falciparum a représenté 80% des infestations paludéennes ayant fait l'objet d'une consultation dans les dispensaires de la région d'étude. Vingt malades présentaient des infestations à *P. malariae* et le reste des infestations à *P. vivax*. La réponse au traitement par la MSP a été excellente; 3207 sujets (96,2%) sur les 3333 qui avaient été suivis après avoir reçu le traitement, présentaient au 7ème jour des frottis négatifs. Sur les 105 malades positifs pour *P. falciparum*, 96 étaient négatifs au 9ème jour, sans traitement complémentaire. On peut donc considérer que le traitement n'a vraiment échoué que chez 0,27% des malades. Chez les 189 malades étudiés au 21e jour, le taux de guérison radicale était de 98,4%, et chez les 1707 malades étudiés au 28e jour, il était de 98,8%. Les effets secondaires ont en général été bénins: vertiges (7,5% des malades), vomissements (5,8%), douleurs abdominales (0,6%), et un malade a présenté un état confusionnel. Les malades ayant vomi dans l'heure qui a suivi la prise du médicament ont reçu une seconde dose normale de MSP, sans présenter d'effets indésirables visibles. La MSP constitue donc un traitement efficace et bien toléré pour le paludisme à falciparum polypharmacorésistant que l'on rencontre à la frontière birmano-thaïlandaise. L'élimination lente du parasite pouvant donner une fausse impression de résistance de type R II, il faut procéder à l'évaluation parasitologique de l'efficacité du médicament au plus tôt une semaine après le traitement.

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